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ART UNIT	PAPER NUMBER
1632	21
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Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary

Application No. 08/486,313	Applicant(s) Weiss et al.
Examiner Hsiu-Ming Saunders	Group Art Unit 1632

- Responsive to communication(s) filed on _____.
- This action is FINAL.
- Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- Claim(s) 26, 27, 32-37, and 39-51 is/are pending in the application.
- Of the above, claim(s) _____ is/are withdrawn from consideration.
- Claim(s) _____ is/are allowed.
- Claim(s) 26, 27, 32-37, and 39-51 is/are rejected.
- Claim(s) _____ is/are objected to.
- Claims _____ are subject to restriction or election requirement.

Application Papers

- See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- The drawing(s) filed on _____ is/are objected to by the Examiner.
- The proposed drawing correction, filed on _____ is approved disapproved.
- The specification is objected to by the Examiner.
- The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- All Some* None of the CERTIFIED copies of the priority documents have been received.
- received in Application No. (Series Code/Serial Number) _____.
- received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
- *Certified copies not received: _____.

- Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- Notice of References Cited, PTO-892
- Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- Interview Summary, PTO-413
- Notice of Draftsperson's Patent Drawing Review, PTO-948
- Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

The amendment filed 3/20/98 (Paper No. 19) has been entered. Applicants' arguments, filed 3/20/98 (Paper No. 19), have been fully considered but they are moot in view of the new ground rejection. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Priority

The priority date for the instant application is 07/08/91 which is the filing date of parent application 07/726,812. The date is determined based on that the written description in the specification discloses the claimed invention of the instant application.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 26, 27, 32-37, and 39-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26, and 37 are vague and indefinite because of the phrase "capable of." "Capable of doing something" means "having potential of doing something but may not be doing it." A growth factor "is capable of" inducingproliferation may or may not be inducing proliferation of cells. Neural stem cells "capable of" producing progeny may or may not be producing progeny.

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It is suggested that applicants delete the phrase "capable of" wherever it is applicable to overcome the rejection. Note that claims 27, 32-37, and 39-51 depend on claim 26.

Claim 27 is vague and indefinite because of the phrase "biological agent." It is not clear where metes and bounds of the biological agent are because the specification does not provide the definition.

Claim 36 is vague and indefinite because of the language "substantially serum-free." It is not clear how the criteria for "substantially serum-free" are set because the specification does not provide its definition. Is a culture medium containing 0.1% serum considered "substantially serum-free ?"

Claim 38 recites the limitation "said population of mammalian neural stem cells ...in (a)" in the claims. There is insufficient antecedent basis for this limitation in the claim.

Claim 40 recites the limitation "said differentiated neural cells" in the claims. There is insufficient antecedent basis for this limitation in the claim.

Claim 27 is vague and indefinite because of the phrase "biological agent." It is not clear where metes and bounds of the biological agent are because the specification does not provide the definition.

Claim 36 is vague and indefinite because of the language "substantially serum-free." It is not clear how the criteria for "substantially serum-free" are set because the specification does not provide its definition. Is a culture medium containing 0.1% serum considered "substantially serum-free ?"

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Claim 40 recites the limitation "said differentiated neural cells" in the claims. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is mostly nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 27 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising the step of *in vitro* genetically modifying neural stem cell progeny to express a polypeptide or protein, does not reasonably provide enablement for a method comprising the step of *in vitro* genetically modifying said neural stem cell progeny to express any and all biological agents.

Claim 27 is directed to a method step comprising *in vitro* genetically modifying neural stem cell progeny to express any and all biological agents.

The scope of the biological agents encompasses agents, heroin, cocaine, barbiturates, Ca²⁺, Na⁺, and K⁺ ions, all of which can produce biological actions on neural cells. Genetic material is known to encode polypeptide or proteins, but not the biological agents like heroin, cocaine, barbiturates, Ca²⁺, Na⁺, or K⁺ ions. Therefore, the specification does not enable genetically modifying neural stem cell progeny to express any and all biological agents.

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The specification discloses genes encoding for the FGF-2 receptor or the NGF receptor (page 71), or the NGF (page 74), or the chromaffin granule amine transporter (CGAT) (page 75). The specification does not disclose genetic material encoding products other than the polypeptide or proteins.

Accordingly, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 26, 32, 34, 39- 42, 47, 51 are rejected under 35 U.S.C. 103 as being unpatentable over Drago et al. (Proc. Natl. Acad. Sci. USA, (1991 Mar 15) 88 (6) 2199-203) in view of Isacson et al. (Exp. Brain Res. (1989) 75 (1) 213-20).

Drago et al. disclose a method of using FGF growth factor for the in vitro proliferation of multipotent neural stem cell and preparation of multipotent neural stem cell progeny (page 2199, left column, last paragraph). The method disclosed by Drago et al. comprises: (a) obtaining a

population of neuroepithelial cells derived from embryonic E10 mice (page 2199, right column, Materials and Methods); (b) preparing a culture medium containing at least one growth factor, FGF, or more growth factors, FGF and IGF-1, capable of inducing cell proliferation (page 2200, right column, Results, first paragraph); (c) preparing a cell culture by combining the cells of (a) with the culture medium of (b) to induce proliferation of cells to produce neural stem cell progeny which includes daughter multipotent neural stem cells. The cells disclosed by Drago et al. contain at least one multipotent neural stem cell because they are derived from embryonic CNS, and it is known the multipotent neural stem cells are present during CNS development (inherent properties). In addition, these cells have characteristics of multipotent stem cells because they are induced by the FGF growth factor to proliferate and differentiate into neurons and glia (page 2199, left column, last paragraph). The teachings of Drago et al. differs from the claimed invention in that they do not disclose transplanting their multipotent neural stem cell progeny to a host. However, at the time the claimed invention was made, Isacson et al. disclosed the step (d), transplanting fetal rat cell suspension from primordial striatum (that inherently contain multipotent neural stem cell progeny, including daughter multipotent neural stem cells and differentiated neural cells) into the lesioned caudate-putamen of the spinal cord (Fig. 1, page 215) of a primate model of Huntington's disease (page 214, left column, last paragraph).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the invention was made to modify the teachings of Drago et al. by implanting multipotent neural stem cell progeny into a host for the benefit of nerual cell replacement in a host, with a reasonable

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expectation of success. Thus, the claimed invention as a whole, was clearly *prima facie* obvious over the collective teachings of the cited reference in the absence of the evidence to the contrary.

Note that the method disclosed by Drago et al. does not enable the survival of their culture system beyond 3 days. Drago et al. disclose that their neural cells at that early stage are not able to be maintained indefinitely in a nondividing state (page 2202, right column, second paragraph). It is noted that the Applicants' method enables *in vitro* proliferation of multipotent neural stem cells beyond 6-8 days, and could be continuously passaged *in vitro* to generate large number of undifferentiated cells. Furthermore, Drago et al. disclosed that their cells grown in medium alone remain dispersed and by 24 hr were mostly nonviable (page 2200, right column, last paragraph). It is noted that the Applicants' method enable the cells from a single neural stem cell cluster to differentiate into neurons, astrocytes, and oligodendrocytes when the growth factors are removed. However, the claim as written, does not distinguish the claimed invention from the prior art.

7. Claim 43 is rejected under 35 U.S.C. 103 as being unpatentable over Drago et al. (Proc. Natl. Acad. Sci. USA, (1991 Mar 15) 88 (6) 2199-203), in view of Isacson et al. (Exp. Brain Res. (1989) 75 (1) 213-20), as applied to claims 26 above, and further in view of Lindvall et al. (Archives of Neurology, (1989 Jun) 46 (6) 615-31).

The teachings of Drago et al. in view of Isacson et al. are as set forth in the previous rejection. The collective teachings of Drago et al. and Isacson et al. differ from the claimed invention in that they do not teach cell transplant into a host's striatum. However, at the time the

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claimed invention was made, Lindvall et al. disclosed implanting neural tissue into the striata in patients (Abstract).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the invention was made to further modify the combined teachings of Drago et al. and Isacson et al. by implanting neural stem cells into striatum for the benefits of neuronal replacement in the striata, with a reasonable expectation of success. Thus, the claimed invention as a whole, was clearly *prima facie* obvious over the collective teachings of the cited reference in the absence of the evidence to the contrary.

8. Claim 44 is rejected under 35 U.S.C. 103 as being unpatentable over Drago et al. (Proc. Natl. Acad. Sci. USA, (1991 Mar 15) 88 (6) 2199-203), in view of Isacson et al. (Exp. Brain Res. (1989) 75 (1) 213-20), as applied to claims 26 above, and further in view of Wendt et al. (Exp. Neurology, (1983 Feb) 79 (2) 452-61).

The teachings of Drago et al. in view of Isacson et al. are as set forth in the previous rejection. The collective teachings of Drago et al. and Isacson et al. differ from the claimed invention in that they do not teach cell transplant into a host's hippocampus. However, at the time the claimed invention was made, Wendt et al. disclosed implanting neural tissue into the hippocampus in adult rat (Abstract).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the invention was made to further modify the combined teachings of Drago et al. and Isacson et al. by implanting neural stem cells into the hippocampus for the benefits of neuronal replacement in the

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the hippocampus, with a reasonable expectation of success. Thus, the claimed invention as a whole, was clearly *prima facie* obvious over the collective teachings of the cited reference in the absence of the evidence to the contrary.

9. Claim 45 is rejected under 35 U.S.C. 103 as being unpatentable over Drago et al. (Proc. Natl. Acad. Sci. USA, (1991 Mar 15) 88 (6) 2199-203), in view of Isacson et al. (Exp. Brain Res. (1989) 75 (1) 213-20), as applied to claims 26 above, and further in view of Kesslak et al. (Exp. Neurology, (1986 Dec) 94 (3) 615-26).

The teachings of Drago et al. in view of Isacson et al. are as set forth in the previous rejection. The collective teachings of Drago et al. and Isacson et al. differ from the claimed invention in that they do not teach cell transplant into a host's frontal cortex. However, at the time the claimed invention was made, Kesslak et al. disclosed implanting neural tissue into the frontal cortex in adult rats (Abstract).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the invention was made to further modify the combined teachings of Drago et al. and Isacson et al. by implanting neural stem cells into the frontal cortex for the benefits of neuronal replacement in the frontal cortex, with a reasonable expectation of success. Thus, the claimed invention as a whole, was clearly *prima facie* obvious over the collective teachings of the cited reference in the absence of the evidence to the contrary.

10. Claim 46 is rejected under 35 U.S.C. 103 as being unpatentable over Drago et al. (Proc. Natl. Acad. Sci. USA, (1991 Mar 15) 88 (6) 2199-203), in view of Isacson et al. (Exp. Brain

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Res. (1989) 75 (1) 213-20), as applied to claims 26 above, and further in view of Andres F. (J. Neural Transplantation, (1989) 1 (1) 11-22).

The teachings of Drago et al. in view of Isacson et al. are as set forth in the previous rejection. The collective teachings of Drago et al. and Isacson et al. differ from the claimed invention in that they do not teach cell transplant into a host's parietal cortex. However, at the time the claimed invention was made, Andres F. disclosed implanting neural tissue into the parietal cortex in adult mice (Abstract).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the invention was made to further modify the combined teachings of Drago et al. and Isacson et al. by implanting neural stem cells into the parietal cortex for the benefits of neuronal replacement in the parietal cortex, with a reasonable expectation of success. Thus, the claimed invention as a whole, was clearly *prima facie* obvious over the collective teachings of the cited reference in the absence of the evidence to the contrary.

11. Claim 27 is rejected under 35 U.S.C. 103 as being unpatentable over Drago et al. (Proc. Natl. Acad. Sci. USA, (1991 Mar 15) 88 (6) 2199-203), in view of Isacson et al. (Exp. Brain Res. (1989) 75 (1) 213-20), as applied to claims 26 above, and further in view of Price et al. (Development, (1988 Nov) 104 (3) 473-82) and Federoff et al. (Proc. Natl. Acad. Sci. U S A 89 (5). 1992. 1636-1640).

The teachings of Drago et al. in view of Isacson et al. are as set forth in the previous rejection. The collective teachings of Drago et al. and Isacson et al. differ from the claimed

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invention in that they do not teach genetically modifying neural stem cell progeny to express a biological agent. However, at the time the claimed invention was made, Price et al. disclosed genetically modifying nerual stem cell progeny, progenitor cells to express a marker gene, LacZ. The cells Price et al. disclosed are multipotent neural stem cells because they give rise to neurons and glial cells (Abstract). Furthermore, Federoff et al. disclosed genetically modified neurons expressing a transgene NGF (Abstract).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the invention was made to further modify the combined teachings of Drago et al. and Isacson et al. by genetically modifying neural stem cell progeny to express a biological agent prior to implantation, for the benefits of studying the effect of gene products on the development of nerual stem cells in vivo, with a reasonable expectation of success. Thus, the claimed invention as a whole, was clearly *prima facie* obvious over the collective teachings of the cited reference in the absence of the evidence to the contrary.

Conclusion

Claims 33, 35, 37, 48-50 are free of prior art of record, however, are subject to other rejections.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hsiu-Ming Saunders whose telephone number is (703) 308-9349.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine C. Chambers, can be reached on (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The Fax Center Number is (703) 308-4242 or (703) 305-3014. The faxing of such papers must conform with the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Hsiu-Ming H. Saunders, Ph.D.

April 24, 1998

Jasemine C. Chambers
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SUPERVISORY PATENT EXAMINER
GROUP 1600